Endocrine Journal

ORIGINAL

Advance Publication
doi:10.1507/endocrj.EJ23-0078

Efficacy of testosterone replacement treatment for patients with symptoms of late-onset hypogonadism based on real-world patient satisfaction

Keisuke Ishikawa[1),2)], Akira Tsujimura[2)], Miho Miyoshi[2)], Yuto Miyoshi[2)], Taiki Ogasa[2)], Ippei Hiramatsu[1),2)], Yuka Uesaka[2)], Taiji Nozaki[2)], Masato Shirai[2)], Kazuhiro Kobayashi[3)] and Shigeo Horie[1)]

[1)] *Department of Urology, Juntendo University, Graduate School of Medicine, Tokyo 113-8421, Japan*
[2)] *Department of Urology, Juntendo University Urayasu Hospital, Chiba 279-0021, Japan*
[3)] *D Clinic Tokyo, Tokyo 100-6210, Japan*

Abstract. Late-onset hypogonadism is generally treated with testosterone replacement treatment. However, the efficacy rate of treatment for patients with low testosterone is not clear because patients without low testosterone are also treated in real-world clinical settings. This study comprised 110 men with low testosterone concentration of <3.0 ng/mL who underwent testosterone replacement treatment. Physical factors, laboratory and endocrinologic profiles, and scores of several questionnaires were assessed. Testosterone replacement treatment was performed with intramuscular injection of 250 mg of testosterone esters every 2–4 weeks, and efficacy was judged by patient satisfaction. After confirming efficacy, changes in several factors by the treatment were evaluated. Finally, the comparison between evaluation by patient satisfaction and by that with the questionnaires was assessed. Among the 110 patients, 77 (70.0%) were satisfied with the treatment, which was effective in 65.7%, 71.4%, and 73.1% of patients with mental, physical, and sexual dysfunction, respectively. The questionnaire scores including the Aging Males Symptoms rating scale were significantly improved in both the satisfaction and non-satisfaction group. However, no significant differences in the amount of change in questionnaire scores were found for all questionnaire scores improved by testosterone replacement treatment between the groups. Patient satisfaction was not associated with improvement of the Aging Males Symptoms score. Although testosterone replacement treatment was effective for 70.0% of the hypogonadal patients, patient satisfaction did not correlate with improvement of questionnaire scores. We concluded that not only questionnaire results but also patient satisfaction is important when evaluating efficacy in patients undergoing testosterone replacement treatment.

Key words: Aging Males Symptoms rating scale, Effective rate, Late-onset hypogonadism, Patient satisfaction, Testosterone replacement treatment

TESTOSTERONE plays an important role physiologically in several organs and tissues in which androgen receptors locate, such as skin, muscle, liver, bone and bone marrow, brain, and sexual organs [1]. Recently, the concept of late-onset hypogonadism (LOH), defined as "a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels" by the European Association of Urology (EAU) and others, has gained increased attention in the current aging society because testosterone decreases gradually as a part of the aging process [2]. In general, characteristic symptoms of LOH include mental symptoms such as depression, anger, and lack of concentration; physical symptoms such as fatigue, a decrease in lean body mass with associated decrease in muscle volume and strength, a decrease in bone mineral density resulting in osteoporosis, increased body fat, and diabetes; and sexual symptoms such as decreasing sexual desire and erectile

Submitted Feb. 22, 2023; Accepted May 12, 2023 as EJ23-0078
Released online in J-STAGE as advance publication Jun. 21, 2023
Correspondence to: Akira Tsujimura, Department of Urology, Juntendo University Urayasu Hospital, 2-1-1 Tomioka, Urayasu, Chiba 279-0021, Japan.
E-mail: atsujimu@juntendo.ac.jp
Abbreviations & Acronyms: AMS, Aging Males Symptoms rating scale; BDI, Beck Depression Inventory; BMI, body mass index; EAU, European Association of Urology; EHS, Erection Hardness Score; FSH, follicle-stimulating hormone; IPSS, International Prostate Symptom Score; LH, luteinizing hormone; LOH, late-onset hypogonadism; NSG, non-satisfaction group; SG, satisfaction group; SHIM, Sexual Health Inventory for Men; TRT, testosterone replacement treatment

dysfunction [3-7]. We have usually treated middle-aged to elderly patients complaining of at least one of the above-listed symptoms with testosterone replacement treatment (TRT) when their serum concentration of testosterone was low. However, along with the high recognition of LOH, two major issues have been highlighted: one is the rate of effectiveness of TRT, and the other is evaluation of the efficacy of TRT.

Regarding the former, only two studies have reported on the rate of treatment effectiveness for patients with symptoms of LOH. One study showed a rate of effectiveness of 63.8% for the treatment in patients with symptoms of LOH [8]. However, that study included patients treated not only with TRT but also with herbal medicine. In addition, the judgement of treatment efficacy in that study was not defined clearly. The other study showed that the rate of effectiveness for patients with symptoms of LOH, whose median serum testosterone concentration was within normal limits (3.64 ± 1.34 ng/mL) was 70.9% [9]. However, those patients were treated with herbal medicine and not by TRT. Until the present study, to our knowledge, no study has reported the rate of effectiveness of TRT for patients with symptoms of LOH as judged by patient satisfaction.

Regarding the latter, improvement of the Aging Males Symptoms rating scale (AMS) score has been used clinically and in several meta-analyses [10, 11]. The AMS is actually recommended by the American Endocrine Society [12] and is generally used in many facilities in Japan. In addition, questionnaires such as the Beck Depression Inventory (BDI) for mental symptoms, Sexual Health Inventory for Men (SHIM), and Erection Hardness Score (EHS) for sexual symptoms have been used supplementarily. Although many reports showed that TRT improved the score of each questionnaire, no reports have examined the relationship between patient satisfaction with TRT and improvement in each of the questionnaires [13-15].

In the present study, we thus aimed to clarify the rate of effectiveness of TRT in patients with low serum testosterone concentration based on patient satisfaction. We further compared the metabolic, endocrinological, and symptomatic characteristics before and after TRT. Finally, we investigated the relationship between patient satisfaction and improvement of the questionnaire scores after TRT by two comparative strategies.

Materials and Methods

This study comprised 110 men who visited our hospital or affiliated clinic between March 2012 and March 2018 and had undergone TRT. We set the critical cutoff value of low testosterone concentration for the indication of TRT at 3.0 ng/mL in reference to the guideline of the American Urological Association and Endocrine Society [16, 17]. They suggest the presence of at least one symptom of LOH as follows: lethargy, general fatigue, malaise, depression, insomnia, frustration, reduced concentration, sweating, hot flashes, coldness, tinnitus, headache, numbness, dizziness, stiff shoulder, night sweats, sexual dysfunction, and decreased libido. All blood samples were collected between 09:00 and 11:00 to monitor endocrinological variables before and after TRT considering the fact that testosterone levels depend on the timing after injection. Blood testosterone levels taper off after injection of testosterone. As most of the patients at our institution continued injections at 4-week intervals, we basically performed blood sampling at the second week after injection to evaluate the average value over the interval period [18]. Physical and laboratory data included age, body mass index (BMI; body weight [kg]/height^2 [m^2]), serum concentrations of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, uric acid, fasting blood sugar, and hemoglobin A1c. Endocrinologic data, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, prolactin, dehydroepiandrosterone sulfate, insulin-like growth factor 1, insulin, and cortisol were also evaluated. LH, FSH, and testosterone were measured by radioimmunoassay. Prolactin, IGF-1, and cortisol were measured by electrochemiluminescence immunoassay. DHEA-S and insulin were measured by chemiluminescent enzyme immunoassay. We assessed symptoms by several specific questionnaires including the IPSS for voiding symptoms, the BDI for depression, the SHIM and EHS for sexual function, and the AMS for LOH. Patients with suspected severe endocrine and metabolic disease or mental disease were excluded. TRT consisted of intramuscular injection of 250 mg of testosterone esters every 2–4 weeks for 3 months according to the clinical practice manual for LOH syndrome by the Japanese Urological Association and the Japanese Society of Men's Health [19]. Efficacy was judged based on patient determination of satisfaction or lack thereof at 3 months after TRT. Patient satisfaction was solely assessed in an interview between the attending physician and the patients. Patients were asked during the treatment decision period, "Were you happy with this treatment?" and the satisfaction level was evaluated based on their answer. If patient satisfaction was equivocal, TRT was judged as being ineffective. Satisfied patients were defined as the satisfaction group (SG), and unsatisfied patients and/or patients lost to follow-up within 3 months were defined as the non-satisfaction group (NSG). Improvement based on the AMS was assessed by a decrease in the AMS score of ≥8 points,

which was the middle value of the change in AMS score in all patients.

First, we calculated the rate of effectiveness of TRT. Second, we compared the metabolic and endocrinological as well as symptomatic characteristics before and after TRT in both the SG and NSG. Third, we compared the change in the scores of all questionnaires between the SG and the NSG. Fourth, we compared the ratio of patient satisfaction between the group with successful treatment as assessed by a change in the AMS score of ≥8 points and the group with failed treatment as assessed by a change in the AMS score of ≤7 points.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and written informed consent was obtained from all patients. The procedures were approved by the Regional Ethics Committee of Juntendo Urayasu Hospital, Urayasu, Japan (approval no. 2018-029) and the D Clinic Tokyo for men.

Statistical analysis

Data and scores of the questionnaires are presented as the mean ± standard error. The paired *t*-test was used to compare these factors before and after TRT in the SG and NSG. The relation between patient satisfaction and the change in the AMS score was assessed with the Mann-Whitney *U* test and Chi-squared test. Statistical significance was set at $p < 0.05$. Statistical analyses were conducted with SPSS version 24.0 (SPSS, Chicago, IL, USA).

Results

Patients' characteristics are summarized in Table 1. The chief complaints of the patients, if we presume to choose three, although symptoms were usually complicated and overlapping, were mental function in 35 patients (31.8%), physical function in 49 patients (44.6%), and sexual function in 26 patients (23.6%). Mean patient age was 53.5 years and BMI was 25.1 kg/m^2. The mean concentrations of all laboratory values were within normal limits, whereas those of the endocrinologic values varied widely. The mean serum testosterone was 2.2 ± 0.6 ng/mL. From the questionnaires, lower urinary tract symptoms were moderate as evaluated by the mean IPSS score of 8.6. Severity of depression was categorized as mild mood disturbance based on the mean BDI score of 16.2. Erectile dysfunction was categorized as moderate based on the mean scores of the SHIM and EHS of 9.7 and 2.2, respectively. The mean AMS score of 46.9 was considered moderate, and the mental, physical, and sexual subscores were 12.7, 19.1, and 15.1, respectively.

Table 1 Characteristics of the 110 patients

	Value	Range
Number of cases	110	
Chief complaint		
Mental symptom	35 (31.8%)	
Physical symptom	49 (44.6%)	
Sexual dysfunction	26 (23.6%)	
Age (y)	53.5 ± 8.7	(40–86)
BMI (kg/m^2)	25.1 ± 3.7	(16.0–37.0)
Total cholesterol (mg/dL)	213.2 ± 53.0	(122–546)
HDL cholesterol (mg/dL)	56.8 ± 14.5	(27–102)
LDL cholesterol (mg/dL)	122.2 ± 36.7	(15–245)
Triglyceride (mg/dL)	218.0 ± 399.5	(37–3,556)
UA (ng/dL)	6.1 ± 1.3	(2.5–10.7)
FBS (mg/dL)	99.4 ± 19.6	(78–201)
HbA1c (%)	5.7 ± 0.6	(4.9–8.6)
LH (mIU/mL)	3.6 ± 4.2	(0.1–24.8)
FSH (mIU/mL)	8.1 ± 8.9	(0.1–55.4)
Testosterone (ng/mL)	2.2 ± 0.6	(0.3–2.9)
Prolactin (ng/mL)	10.8 ± 12.4	(0.3–82.9)
DHEA-S (μg/dL)	213.5 ± 94.9	(24–490)
IGF-1 (ng/mL)	140.5 ± 44.3	(62–374)
Insulin (μU/mL)	6.5 ± 4.2	(0.6–22.2)
Cortisol (μg/dL)	9.9 ± 3.9	(0.8–21.0)
IPSS	8.6 ± 5.8	(0–26)
BDI	16.2 ± 9.4	(1–42)
SHIM	9.7 ± 6.6	(1–25)
EHS	2.2 ± 1.2	(1–4)
AMS		
Total	46.9 ± 12.1	(26–80)
Mental subscore	12.7 ± 5.1	(5–25)
Physical subscore	19.1 ± 5.2	(7–33)
Sexual subscore	15.1 ± 4.4	(5–25)

AMS, Aging Males Symptoms; BDI, Beck Depression Inventory; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; EHS, Erection Hardness Score; FBS, fasting blood sugar; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IPSS, International Prostate Symptom Score; LDL, low-density lipoprotein; LH, luteinizing hormone; SHIM, Sexual Health Inventory for Men; UA, uric acid.

Findings before and after TRT in the SG and NSG can be compared in Tables 2 and 3. Among the 110 patients, 77 (effectiveness rate of 70.0%) were classified into the SG. TRT was effective in 23 patients (65.7%), 35 patients (71.4%), and 19 patients (73.1%), with mental, physical, and sexual dysfunction. In the SG, serum testosterone increased significantly from 2.2 to 4.6 ng/mL. With respect to LOH-related symptoms, the BDI, SHIM, and AMS scores improved significantly,

Table 2 Endocrinological variables and questionnaires before and after TRT

	Satisfaction group ($N = 77$; 70.0%)		p-value
	Before	After	
Total cholesterol (mg/dL)	215.9 ± 57.6	214.9 ± 77.1	0.925
HDL cholesterol (mg/dL)	56.9 ± 15.1	65.5 ± 17.1	0.4
LDL cholesterol (mg/dL)	124.6 ± 36.2	112.3 ± 14.8	0.753
Triglyceride (mg/dL)	224.1 ± 465.0	226.4 ± 486.0	0.202
UA (ng/dL)	5.9 ± 1.3	5.2 ± 1.4	0.463
FBS (mg/dL)	98.5 ± 19.7	101.6 ± 20.5	0.08
HbA1c (%)	5.7 ± 0.6	5.5 ± 0.3	0.236
LH (mIU/mL)	3.8 ± 4.6	3.2 ± 4.0	0.025
FSH (mIU/mL)	8.5 ± 9.7	9.1 ± 13.1	0.028
Testosterone (ng/mL)	2.2 ± 0.7	4.6 ± 3.1	0.001
Prolactin (ng/mL)	10.5 ± 11.7	11.1 ± 4.3	0.043
DHEA-S (μg/dL)	210.3 ± 96.7	132.8 ± 67.5	0.753
IGF-1 (ng/mL)	141.1 ± 37.7	112.8 ± 41.5	0.674
Insulin (μU/mL)	6.6 ± 4.6	18.0 ± 29.1	0.001
Cortisol (μg/dL)	9.7 ± 3.8	9.8 ± 3.9	0.663
IPSS	9.1 ± 6.0	8.4 ± 5.6	0.098
BDI	16.7 ± 9.5	10.7 ± 8.6	0.001
SHIM	9.2 ± 6.4	13.0 ± 7.6	0.002
EHS	2.2 ± 1.3	2.8 ± 0.9	0.041
AMS			
Total	47.9 ± 11.7	39.6 ± 13.1	0.001
Mental subscore	13.1 ± 5.1	11.6 ± 4.6	0.241
Physical subscore	19.5 ± 5.1	16.0 ± 5.6	0.001
Sexual subscore	15.2 ± 4.4	11.9 ± 4.1	0.001

AMS, Aging Males Symptoms; BDI, Beck Depression Inventory; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; EHS, Erection Hardness Score; FBS, fasting blood sugar; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IPSS, International Prostate Symptom Score; LDL, low-density lipoprotein; LH, luteinizing hormone; SHIM, Sexual Health Inventory for Men; TRT, testosterone replacement treatment; UA, uric acid.

whereas no significant improvement was observed in the IPSS. In the NSG, serum testosterone also significantly increased from 2.2 to 3.4 ng/mL. The symptom scores of the BDI, SHIM, and AMS also improved significantly similar to those in the SG, and no significant improvement was observed in the IPSS.

The relationship between patient satisfaction and improvement of the questionnaire scores after TRT is shown in Fig. 1. No significant differences in the amount of change in the BDI, SHIM, and AMS scores were found between the SG and NSG. We classified the group with improvement of the AMS (by ≥8 points) and the group with no improvement of the AMS (by ≤7 points) according to the amount of change in the AMS and determined the ratio of patient satisfaction with TRT in each patient group. Thirty-nine patients (65.0%) were satisfied with TRT, even for the group with improvement of the AMS (by ≥8 points). Nevertheless, as many as 38 patients (76.0%) in the group with no improvement of the AMS (by ≤7 points) were satisfied with TRT (Table 4). Therefore, patient satisfaction did not appear to be associated with improvement of the AMS score.

Discussion

Some reports have shown that TRT improved mood and depression among mental symptoms, [20] increased bone and mineral density [21] and lean body mass, and decreased body fat among physical symptoms, [22] and improved erectile function and libido among sexual symptoms in patients with low serum testosterone concentrations [23]. Although these merits of TRT have been well accepted in the field of urology, the true rate of effectiveness of TRT still remains unclear because most

Table 3 Endocrinological variables and questionnaires before and after TRT

	Non-satisfaction group (N = 33; 30.0%)		p-value
	Before	After	
Total cholesterol (mg/dL)	207.1 ± 40.9	201.4 ± 36.9	0.572
HDL cholesterol (mg/dL)	56.5 ± 13.4	52	0.317
LDL cholesterol (mg/dL)	116.4 ± 37.6	147	0.317
Triglyceride (mg/dL)	204.0 ± 172.6	166.2 ± 72.7	0.9
UA (ng/dL)	6.6 ± 1.3	6.6	0.317
FBS (mg/dL)	101.4 ± 19.6	100.1 ± 9.1	0.533
HbA1c (%)	5.8 ± 0.8	6.9	0.317
LH (mIU/mL)	3.0 ± 3.0	2.0 ± 1.7	0.57
FSH (mIU/mL)	7.1 ± 6.8	2.8 ± 1.1	0.655
Testosterone (ng/mL)	2.2 ± 0.5	3.4 ± 1.7	0.006
Prolactin (ng/mL)	11.3 ± 14.2	8.63	0.317
DHEA-S (μg/dL)	221.1 ± 91.5	102	0.317
IGF-1 (ng/mL)	141.1 ± 37.7	90	0.317
Insulin (μU/mL)	6.2 ± 3.2	13.9 ± 11.4	0.001
Cortisol (μg/dL)	10.3 ± 4.1	11.9 ± 3.3	0.65
IPSS	7.5 ± 5.1	5.5 ± 5.6	0.082
BDI	14.8 ± 9.2	8.5 ± 8.6	0.015
SHIM	10.9 ± 7.1	13.3 ± 7.1	0.046
EHS	2.3 ± 1.1	2.6 ± 1.3	0.124
AMS			
Total	44.5 ± 13.0	34.3 ± 8.9	0.005
Mental subscore	11.8 ± 4.9	8.5 ± 3.2	0.023
Physical subscore	18.0 ± 5.5	13.9 ± 3.6	0.032
Sexual subscore	14.7 ± 4.6	12.0 ± 4.8	0.015

AMS, Aging Males Symptoms; BDI, Beck Depression Inventory; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; EHS, Erection Hardness Score; FBS, fasting blood sugar; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; IPSS, International Prostate Symptom Score; LDL, low-density lipoprotein; LH, luteinizing hormone; SHIM, Sexual Health Inventory for Men; TRT, testosterone replacement treatment; UA, uric acid.

studies have been conducted based on the improvement of symptoms scores of questionnaires such as the AMS, and physical improvement such as that in bone mineral density, lean body mass, muscle strength, and exercise capacity. Here, we clearly showed that the rate of effectiveness was 70.0% in patients with low serum testosterone concentration and with symptoms of LOH treated by TRT. Interestingly, this rate of effectiveness was very similar to that of the previous study using treatment with herbal medicine (70.9%) [9]. Because neither the previous study nor ours had placebo arms, the data from these studies raised our suspicion that around 70% of patients might be satisfied when any kind of treatment intervention was performed. However, we believe that our finding showing that TRT is effective for 70.0% of patients with low serum testosterone and at least one of the symptoms of LOH is valuable in the real-world clinical setting.

In the present study, we also showed that TRT was effective in 65.7%, 71.4%, and 73.1% of our patients with mental, physical, and sexual dysfunction as assessed by patient satisfaction. One report showed that only three symptoms (decreased frequency of sexual activity, decreased morning erection, and decreased libido) were closely associated with testosterone levels among the symptoms of LOH [24]. This suggests that the increase of testosterone levels by TRT may be most expected to cure the sexual symptoms. In addition, because mental symptoms are surely affected by not only serum testosterone level but also several environment factors including social stress in today's complicated modern society, the rate of effectiveness of TRT for mental symptoms was the lowest. We also clearly showed that the scores of the BDI, SHIM, and AMS improved

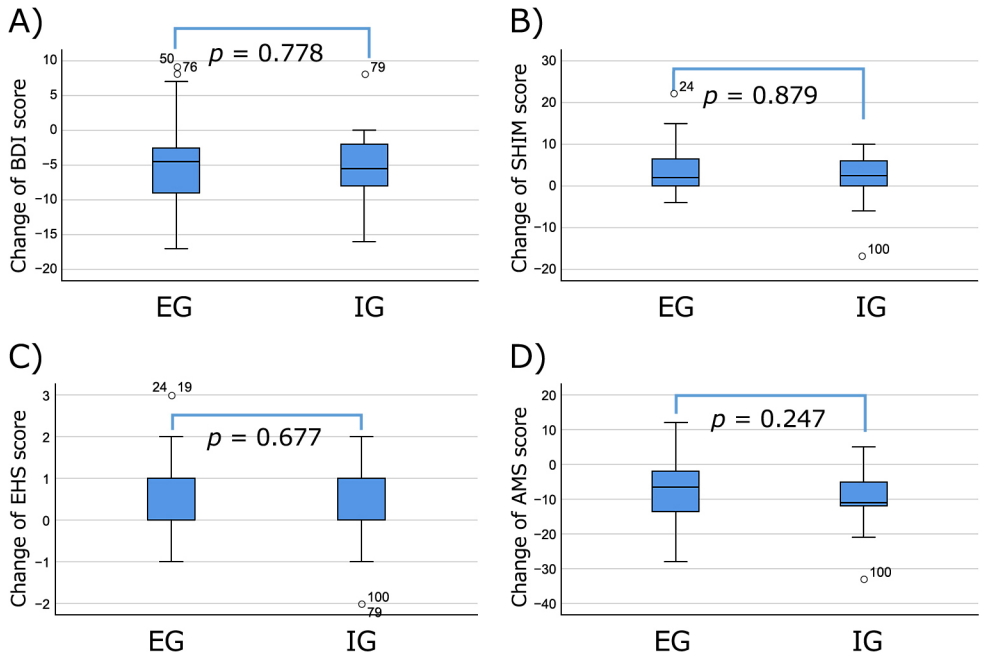

Fig. 1 Comparison of the change of four ratings scores between the satisfaction group (SG) and the non-satisfaction group (NSG). A) BDI, Beck Depression Inventory; B) SHIM, Sexual Health Inventory for Men; C) EHS, Erection Hardness Score; and D) AMS, Aging Males Symptoms rating scale.

Table 4 Relationship between change in AMS score and patient satisfaction after TRT

	Patients' complaints		*p*-value
	Satisfied	Unsatisfied	
Change in AMS score			
8≤ (*N* = 60)	39 (65.0%)	21 (35.0%)	0.21
≥7 (*N* = 50)	38 (76.0%)	12 (24.0%)	

AMS, Aging Males Symptoms rating scale; TRT, testosterone replacement treatment.

significantly from before to after TRT regardless of whether the patients were in the SG or NSG.

Regarding symptoms of LOH, many studies have assessed results based on the improvement of the AMS. Several randomized controlled studies to assess the efficacy of TRT were conducted based on change in the AMS [25, 26]. The AMS is definitely the most commonly used scale worldwide to measure health-related quality of life and symptoms in aging males. The scale is a self-administered questionnaire whose response categories for all 17 questions are assigned score points. At present, the AMS is accepted as a valuable tool for assessing symptoms of LOH in patients. However, the change in the AMS score as well that in the other questionnaires did not differ significantly between the SG and NSG. Furthermore, we also showed that the rate of patient satisfaction with TRT did not differ between the groups in terms of successful or failed treatments from the viewpoint of the change in the AMS score. These findings are consistent with a previous study with Japanese patients showing that the AMS score worsened in 28.2% of the patients who were satisfied with TRT based on the patients' chief complaints, whereas among the patients who showed improvement in the AMS score, as many as 69.6% were not fully satisfied with TRT [27]. In the present study as well, 35.0% of the patients whose AMS score improved by 8 points or more were not satisfied with TRT, whereas 76.0% of the patients whose AMS score was improved by 7 points or less were satisfied with TRT. The reasons for those who were not satisfied with TRT are not clear, but we assume that they probably had excessive expectations of TRT that were not met.

These previous findings and ours suggested that patient satisfaction with TRT and changes in the questionnaire scores do not correlate, and an improvement in the AMS score does not guarantee symptom relief. We want to emphasize that it is most important for patients to be satisfied with their treatment in the real-world clinical setting because LOH is a quality-of-life disease in males.

The present study has some limitations. First, we conducted blood tests to determine the biochemical and endocrinological profiles only once. Such testing, especially the endocrinological profile, should be repeated because recent studies have shown that testosterone is secreted seasonally and diurnally [28]. Second, we could

not check life-style factors including smoking, alcohol drinking, sleeping status, and exercise due to this being a retrospective study. However, medications were not changed and/or added during the treatment. Third, the 3-month observation period was short and continuing TRT might change the results. Although these limitations cannot be ignored, we believe that our findings represent the current situation in a real-world clinical setting. Further long-term observation with a placebo arm will be needed to resolve these issues.

In conclusion, this is the first study, to our knowledge, to investigate the rate of effectiveness of TRT in patients with low serum testosterone concentration and with at least one symptom of LOH. We clearly showed that TRT was effective in 70.0% of the patients and that TRT was effective in 65.7%, 71.4%, and 73.1% of the patients with mental, physical, and sexual dysfunction. There were significant improvements in the total scores of the BDI, SHIM, and AMS both in the SG and the NSG. However, we also found that patient satisfaction did not correlate with the improvement in questionnaire scores, even with that of the AMS, and that an improvement in the AMS score does not guarantee symptom relief.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

References

1. Tsujimura A, Hiramatsu I, Aoki Y, Shimoyama H, Mizuno T, *et al.* (2017) Atherosclerosis is associated with erectile function and lower urinary tract symptoms, especially nocturia, in middle-aged men. *Prostate Int* 5: 65–69.
2. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, *et al.* (2008) Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. *Eur J Endocrinol* 159: 507–514.
3. Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, *et al.* (2007) Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 92: 4241–4247.
4. Bondy CA (2006) Endogenous sex hormones and type 2 diabetes risk. *JAMA* 296: 169.
5. Kawano H, Sato T, Yamada T, Matsumoto T, Sekine K, *et al.* (2003) Suppressive function of androgen receptor in bone resorption. *Proc Natl Acad Sci U S A* 100: 9416–9421.
6. Mauras N, Hayes V, Welch S, Rini A, Helgeson K, *et al.* (1998) Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. *J Clin Endocrinol Metab* 83: 1886–1892.
7. Page ST, Herbst KL, Amory JK, Coviello AD, Anawalt BD, *et al.* (2005) Testosterone administration suppresses adiponectin levels in men. *J Androl* 26: 85–92.
8. Taniguchi H, Matsuda T (2017) Multi-institutional survey of medical treatment for late-onset hypogonadism in Japan. *Am J Mens Health* 11: 376–379.
9. Michihara S, Shin N, Watanabe S, Morimoto Y, Okubo T, *et al.* (2013) A Kampo formula, saikokaryukotsuboreito, improves serum testosterone levels of castrated mice and its possible mechanism. *Aging Male* 16: 17–21.
10. Nian Y, Ding M, Hu S, He H, Cheng S, *et al.* (2017) Testosterone replacement therapy improves health-related quality of life for patients with late-onset hypogonadism: a meta-analysis of randomized controlled trials. *Andrologia* 49: e12630.
11. Guo C, Gu W, Liu M, Peng BO, Yao X, *et al.* (2016) Efficacy and safety of testosterone replacement therapy in men with hypogonadism: a meta-analysis study of placebo-controlled trials. *Exp Ther Med* 11: 853–863.
12. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, *et al.* (2010) Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 95: 2536–2359.
13. Aydogan U, Aydogdu A, Akbulut H, Sonmez A, Yuksel S, *et al.* (2012) Increased frequency of anxiety, depression, quality of life and sexual life in young hypogonadotropic hypogonadal males and impacts of testosterone replacement therapy on these conditions. *Endocr J* 59: 1099–1105.
14. Shigehara K, Konaka H, Sugimoto K, Nohara T, Izumi K, *et al.* (2018) Sleep disturbance as a clinical sign for severe hypogonadism: efficacy of testosterone replacement therapy on sleep disturbance among hypogonadal men without obstructive sleep apnea. *Aging Male* 21: 99–105.
15. Okada K, Miyake H, Ishida T, Sumii K, Enatsu N, *et al.* (2018) Improved lower urinary tract symptoms associated with testosterone replacement therapy in Japanese men with late-onset hypogonadism. *Am J Mens Health* 12: 1403–1408.
16. Park HJ, Ahn ST, Moon DG (2019) Evolution of guidelines for testosterone replacement therapy. *J Clin Med* 8: 410.
17. Salter CA, Mulhall JP (2019) Guideline of guidelines: testosterone therapy for testosterone deficiency. *BJU Int* 124: 722–729.
18. Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, *et al.* (2005) Investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male* 8: 56–58.
19. Namiki M, Akaza H, Shimazui T, Ito N, Iwamoto T, *et*

al. (2008) Clinical practice manual for late-onset hypogonadism syndrome. *Int J Urol* 15: 377–388.
20. Hong JH, Ahn TY (2002) Oral testosterone replacement in Korean patients with PADAM. *Aging Male* 5: 52–56.
21. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, *et al.* (1999) Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 84: 1966–1972.
22. Boyanov MA, Boneva Z, Christov VG (2003) Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 6: 1–7.
23. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS (2002) The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab* 87: 1467–1472.
24. Liu ZY, Zhou RY, Lu X, Zeng Q, Wang H, *et al.* (2016) Identification of late-onset hypogonadism in middle aged and elderly men from a community of China. *Asian J Androl* 18: 747–753.
25. Legros JJ, Meuleman EJ, Elbers JM, Geurts TB, Kaspers MJ, *et al.* (2009) Oral testosterone replacement in symptomatic late-onset hypogonadism: effects on rating scales and general safety in a randomized, placebo-controlled study. *Eur J Endocrinol* 160: 821–831.
26. Ho CC, Tong SF, Low WY, Ng CK, Khoo EM, *et al.* (2012) A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. *BJU Int* 110: 260–265.
27. Miyagawa Y, Fukuhara S, Soda T, Takezawa K, Kiuchi H, *et al.* (2015) Perspective of the efficacy of androgen replacement therapy for late-onset hypogonadism from Osaka University experience. *Jpn J Urol Surg* 28: 69–71 (In Japanese).
28. Kim MK, Zhao C, Kim SD, Kim DG, Park JK (2012) Relationship of sex hormones and nocturia in lower urinary tract symptoms induced by benign prostatic hyperplasia. *Aging Male* 15: 90–95.